Neuropsychologia 48 (2010) 1096–1103

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

# Medication impairs probabilistic classification learning in Parkinson's disease

Marjan Jahanshahi[a,*], Leonora Wilkinson[a], Harpreet Gahir[b], Angeline Dharminda[b], David A. Lagnado[b]

[a] Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, Queen Square, London, WC1N 3 BG, United Kingdom
[b] Department of Psychology, UCL, Gower Street, London, United Kingdom

ARTICLE INFO

*Article history:*
Received 14 May 2009
Received in revised form
20 November 2009
Accepted 7 December 2009
Available online 16 December 2009

*Keywords:*
Parkinson's disease
Learning
Levodopa
Dopamine
Basal ganglia

ABSTRACT

In Parkinson's disease (PD), it is possible that tonic increase of dopamine associated with levodopa medication overshadows phasic release of dopamine, which is essential for learning. Thus while the motor symptoms of PD are improved with levodopa medication, learning would be disrupted. To test this hypothesis, we investigated the effect of levodopa medication on learning on the weather prediction task (WPT), which involves probabilistic classification learning. 11 PD patients and 13 matched controls completed 200 trials of the WPT, with the patients either on or off their usual levodopa medication. Consistent with prior studies, when PD patients were assessed on medication, overall WPT performance was significantly worse than controls. However, when these patients were studied following withdrawal from medication, overall performance was equivalent to controls, and significantly better than when on medication. The significant deterioration of learning on the WPT in PD patients when on compared to off medication supports the proposal that tonic increase of dopamine with dopaminergic medication masks phasic changes in dopamine release essential for learning. These results highlight the need for careful 'titration' of dopaminergic medication to produce the desired improvement of the motor symptoms without the associated detrimental effects on cognition and learning.



The WPT is a non-motor probabilistic classification task involving incremental learning over many trials considered to occur without any explicit knowledge (Knowlton, Squire, & Gluck, 1994). On each trial, participants are presented with a particular arrangement of tarot cards each with distinct patterns. On each trial, participants use the card arrangement to predict a binary outcome: whether the weather will be rainy or fine. Each of the four cards is independently associated with the two possible outcomes with a fixed probability, although participants are not explicitly informed about this. Knowlton, Mangels, and Squire (1996) reported a double dissociation on the WPT: for amnesics learning on the WPT was equivalent to healthy controls but they had no recollection of the stimuli or the learning episode; whereas patients with PD with striatal dysfunction were significantly impaired in learning on the WPT but nevertheless had good recognition of the stimuli and the testing episode. The specificity of deficits to striatal dysfunction was further confirmed by normal WPT learning by patients with frontal lesions (Knowlton, Mangels, et al., 1996) and those with cerebellar disease (Witt, Nuhsman, & Deuschl, 2002), and impaired learning by patients with Huntington's disease (Knowlton, Squire, et al., 1996). Other studies, however, have revealed learning deficits on the WPT and a parallel version of it in patients with bilateral hippocampal damage due to hypoxia (Hopkins, Myers, Shohamy, Grossman, & Gluck, 2004; Meeter, Talamini, Schmitt, & Riedel, 2006). Consistent with the results of the studies in clinical populations, imaging work has demonstrated involvement of both the basal ganglia and medial temporal lobes (MTL) in learning during the WPT, although the time course of their involvement in learning is different and they show different sensitivity to distraction under dual task conditions, suggesting that the procedural and declarative memory systems compete or interact during learning on this task (Aron, Robbins, & Poldrack, 2004; Foerde, Knowlton, & Poldrack, 2006; Poldrack et al., 2001; Poldrack, Prabhakaran, Seger, & Gabrieli, 1999; Seger & Cincotta, 2006). On the basis of comparison of patterns of brain activation (Poldrack et al., 2001) and performance of PD patients in the standard feedback-based version of the WPT vs. a paired associate version; it has been further suggested that the feedback element of the WPT is the component that specifically engages the striatum (Poldrack et al., 2001; Shohamy, Myers, Grossman, et al., 2004); although such a selective impairment of learning on the feedback-based WPT relative to the paired associate WPT in PD has not been found in some studies, which reported deficits in learning in medicated PD patients relative to controls on both versions of the task (Wilkinson, Lagnado, Quallo, &

* Corresponding author at: Sobell Department of Motor Neuroscience and Movement Disorders, The National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, 33 Queen Square, London, WC1N 3 BG, United Kingdom. Tel.: +44 0203 108 0033; fax: +44 0207 278 9836.
*E-mail address:* m.jahanshahi@ion.ucl.ac.uk (M. Jahanshahi).

0028-3932/$ – see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.neuropsychologia.2009.12.010

Jahanshahi, 2008). An excellent review of research on the WPT has been recently provided by Shohamy, Myers, Kalanithi, and Gluck (2008).

Dopamine deficiency is the primary hallmark of PD, which results from the loss of dopamine producing cells in the substantia nigra pars compacta which in turn leads to depleted levels of dopamine in the striatum (Hornykiewicz & Kish, 1984). Dopamine replacement therapy with levodopa or dopamine agonist medication remains the single most effective treatment for the motor symptoms of PD. In contrast, in PD levodopa medication has variable effects on cognitive function, improving some aspects of cognition including alternating word fluency (Gotham, Brown, & Marsden, 1988), working memory and cognitive sequencing (Cooper et al., 1992; Shohamy, Myers, Grossman, Sage, & Gluck, 2005) and task switching (Cools, Barker, Sahakian, & Robbins, 2001) but worsening other aspects of cognition including conditional associative learning (Gotham et al., 1988) probabilistic reversal learning (Cools, Altamirano, & D'Esposito, 2006; Cools et al., 2001; Swainson et al., 2000) motor sequence learning (Feigin et al., 2003), incremental learning with feedback (Shohamy, Myers, Geghman, Sage, & Gluck, 2006) and multi-dimensional discrimination learning (Swainson et al., 2006). In light of this, in the present study, our aim was to test the hypothesis that medication impairs learning on the WPT in PD. We used a within-subject repeated measures design, and tested both PD patients on and off medication and matched controls with parallel versions of the WPT on two occasions.

## 1. Methods

### 1.1. Participants

Eleven individuals with a diagnosis of idiopathic PD (8 male) aged between 53 and 73 ($M$ = 63.5, $S.D.$ = 6.2) were studied. Patients were recruited from the Movement Disorders Clinics at the National Hospital for Neurology and Neurosurgery. They met Parkinson's Disease Society Brain Bank diagnostic criteria for PD (Hughes, Daniel, Kilford, & Lees, 1992). Disease duration ranged from 3 to 37 years ($M$ = 13.2, $S.D.$ = 10.7). Stage of illness and severity of the motor symptoms of PD was rated while patients were both on and off their usual medication using the Hoehn and Yahr (H&Y) (1967) scale and the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS, part III). The majority of the sample had mild to moderate disease. When patients were assessed off medication, the mean H&Y rating was 2.8 ($S.D.$ = .6) and the mean UPDRS score was 36.3 ($S.D.$ = 10.0). On medication, the mean H&Y was 2.2 ($S.D.$ = .8) and the mean UPDRS score was 18.0 ($S.D.$ = 10.1). All patients were non-demented as demonstrated by scores > 26 on the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975). Patients were also screened for clinical depression (scores > 18) on the Beck Depression Inventory (BDI) (Beck, Erbaugh, Ward, Mock, & Mendelsohn, 1961) and none were clinically depressed at the time of study, although two were on anti-depressant medication. All patients in this study were treated with levodopa (Sinemet, Madopar) and were responding well and stable on their medication doses. The mean levodopa equivalent daily dose was 821.4 mg ($S.D.$ = 337.3). In addition, patients were receiving dopaminergic and anticholinergic medication. When patients were assessed on medication, they continued to take their usual medication and were tested within 2 h of taking their last dose. In the 'off' state, patients were assessed after overnight withdrawal of medication, after an average of 13.79 ($S.D.$ = 2.2) h off medication. Patients with deep brain stimulation, severe dyskinesias or on-off fluctuations were not included in the study.

Thirteen healthy volunteers (5 male) aged between 44 and 69 ($M$ = 60.0, $S.D.$ = 9.7) took part in the study. Controls were recruited via an advertisement at a local adult education centre. Prior to participation in the study, they were interviewed and screened for suitability. None of the controls had any neurological disorder, psychiatric illness, head injury, or history of alcohol or drug abuse. Further screening of the controls was achieved through completion of the Beck Depression Inventory and the Mini-Mental State Examination, on which the controls had mean scores in the normal range. For both patients and controls, an estimate of current IQ was obtained with the Advanced Progressive Matrices (Raven, 1938). The total time spent in education was determined. Information about the controls and PD patients is presented in Tables 1 and 2.

The study was approved by the Joint Ethics Committee of the Institute of Neurology and The National Hospital for Neurology and Neurosurgery. Informed consent was obtained prior to participation in the study from all controls and PD patients. Control participants were paid a fee of £6 per hour and the traveling expenses of patients were reimbursed.

**Table 1**
Demographic information for patients with Parkinson's disease (PD) and controls and the clinical characteristics of the patients.

| | PD ($n$ = 11) | | Controls ($n$ = 13) | | $p$ |
|---|---|---|---|---|---|
| | Mean | $S.D.$ | Mean | $S.D.$ | |
| Age (years) | 63.5 | 6.2 | 60.0 | 9.7 | .31 |
| Education (years) | 16.5 | 3.4 | 14.6 | 3.2 | .18 |
| IQ estimate | 116.6 | 7.8 | 111.8 | 10.8 | .23 |
| Mini-Mental State Examination (0–30) | 29.1 | 1.1 | 28.7 | 1.5 | .48 |
| Beck Depression Inventory (0–63) | 9.4 | 5.4 | 7.3 | 5.9 | .38 |
| Mean | $S.D.$ | | | | |
| Unified Parkinson's Disease Rating Scale | | | | | |
| On medication | | | | | |
| 18.0 | 10.1 | | | | |
| Off medication | | | | | |
| 36.3 | 10.0 | | | | |
| Hoehn–Yahr Stage of Ilness | | | | | |
| On medication | | | | | |
| 2.2 | .8 | | | | |
| Off medication | | | | | |
| 2.8 | .6 | | | | |
| Disease duration (years) | | | | | |
| 13.2 | 10.7 | | | | |
| Levodopa equivalent daily dose (mg) | | | | | |
| 821.4 | 337.3 | | | | |

### 1.2. The weather prediction task

The stimulus materials were drawn from a set of four tarot cards each with a different geometric pattern (e.g. triangles, circles, diamonds and squares) arranged horizontally across a computer screen. During each of two conditions either; on vs. off medication (PD patients) or time 1 vs. time 2 (controls) participants performed 200 trials of the WPT. On each trial, they were presented with a particular arrangement of cards comprising: one, two or three of the four possible tarot cards. There were 14 possible arrangements of these cards. Each arrangement was associated with one of two outcomes (e.g. rain or fine) and overall these two outcomes occurred equally often. The learning set was constructed such that each individual card was associated with an outcome with a fixed independent probability. For example, the fixed probability that the outcome was rainy was .2 if triangles (card 1) were present, .4 if circles (card 2) were present, .6 if diamonds (card 3) were present and .8 if squares (card 4) were present. The probability assigned to each card was counterbalanced and the probability of an outcome on a particular trial was based on the combined probability of the cards present. The 14 possible card arrangements and the probability of the outcome for each of the 14 patterns were the same as those employed in our previous study (Wilkinson et al., 2008). Over 200 trials, the two outcomes were equally likely to be correct. In sum, two cards were predictive of rainy weather, one strongly (card 4), one weakly (card 3), and two cards were predictive of fine weather, one strongly (card 1), one weakly (card 2). Overall, participants experienced identical arrangement frequencies (order randomized for each participant) but the actual outcomes could differ slightly across participants.

**Table 2**
Medication regimes of individual patients.

| Patient | Medications | Levodopa equivalent daily dose (mg) |
|---|---|---|
| 1 | Levodopa, ropinerole | 1030 |
| 2 | Levodopa, ropinerole | 420 |
| 3 | Levodopa, pergolide, amantadine, amitriptyline | 1200 |
| 4 | Levodopa, pergolide, amantadine | 1080 |
| 5 | Levodopa, ropinerole, amantadine, selegiline, entacapone, amitriptyline, motilium | 840 |
| 6 | Levodopa, ropinerole | 1100 |
| 7 | Levodopa, cabergoline | 830 |
| 8 | Levodopa, amantadine | 350 |
| 9 | Levodopa, amantadine, cabergoline, clonazepam | 795 |
| 10 | Levodopa, entacapone | 1080 |
| 11 | Levodopa, benzhexol | 250 |